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Questa è la Versione finale referata (Post print/Accepted manuscript) della seguente pubblicazione:

*Original Citation:*

Primary cutaneous follicular centre- cell lymphoma- a lymphoproliferative disease with favourable prognosis / N. Pimpinelli; M. Santucci; A. Bosi; S. Moretti; C. Vallecchi; A. Messori; B. Giannotti. - In: CLINICAL AND EXPERIMENTAL DERMATOLOGY. - ISSN 0307-6938. - STAMPA. - 14:(1989), pp. 12-19.

*Availability:*

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## Primary cutaneous follicular centre-cell lymphoma—a lymphoproliferative disease with favourable prognosis

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Accepted for publication 13 July 1988

### Summary

In this study the clinico-pathological and immuno-histological features, the methods of treatment and follow-up data of 11 patients with follicular centre-cell (B-cell) lymphoma primarily presenting in the skin are reported. All the patients had nodular, tumorous and/or papulonodular skin lesions on the trunk. In nine patients the disease was confined to a circumscribed area of the back. Small papulonodular or plaque-like lesions, as well as large nodules or tumours, were biopsied in six of 11 patients. No clear-cut correlation between the age and clinical morphology of the lesions and their histological growth pattern was found. Interestingly, however, a different immuno-architectural pattern was observed in large, late lesions compared to small, early lesions. Initial treatment consisted of orthovolt radiotherapy (in two patients associated with surgical excision), resulting in complete remission in all patients. Only one patient developed extracutaneous disease, which was limited to a single drainage lymph node appearing simultaneously with a cutaneous relapse. Five other patients had recurrent disease in the skin close to the initial site. The median disease-free period was 15.5 months. On relapse, radiotherapy alone or in combination with short courses of chemotherapy was performed. This resulted in a second complete remission. All the patients are still alive and in complete remission, with a median survival of 37 months. These results confirm the favourable prognosis of patients affected with primary cutaneous follicular centre-cell lymphoma limited to the trunk. Orthovolt radiotherapy proved to be the most suitable treatment for both initial lesions and relapses limited to the skin.

The non-Hodgkin's lymphomas (NHL) comprise a group of primary neoplasms of the lymphoreticular tissue

involving lymphoid cells in various degrees of differentiation. This is antigen-independent and occurs mainly in lymphomas of children and young adults generally arise from lymphocyte precursor cells in their primary differentiation. This is antigen-independent and occurs mainly in the bone marrow and thymus. In adults, NHL are usually the neoplastic counterparts of the immuno-competent cells in secondary, antigen-dependent differentiation, occurring mainly in the spleen and lymph nodes.<sup>1</sup> Moreover, NHL may develop in extranodal organs and the proliferation may be related to physiological extranodal lymphocytic migration within the normal immune system.<sup>2</sup> The primary localization of NHL in extranodal sites is well known and relatively frequent.<sup>3</sup> The skin is the third most common site for extranodal NHL.<sup>4,5</sup> Excluding mycosis fungoides (MF) and Sézary syndrome, cutaneous lymphomas have long been considered manifestations of the systemic spread of lymphoreticular neoplasia arising in lymphoid organs and have been associated with an unfavourable prognosis.<sup>6,7</sup> Recent studies have suggested that cutaneous lymphomas other than MF are much less rare than previously estimated.<sup>8-10</sup> They are mostly of B-cell origin<sup>8</sup> but an increasing number of T-cell lymphomas other than MF have been reported.<sup>11-13</sup> Furthermore, patients with disease limited to the skin seem to have a much better prognosis compared to patients with extracutaneous involvement.<sup>11</sup>

In this report, a series of 11 patients with follicular centre-cell lymphoma primarily presenting in the skin is evaluated. These lymphomas had the clinical and pathological features of Crosti's reticulohistiocytoma, a defined lymphoproliferative disorder. This disorder is characterized by: the development of localized papulonodular or tumorous skin lesions preferentially located on the back; onset in middle or old age; a higher incidence in males; a slowly progressive but favourable course; and marked radiosensitivity.<sup>14</sup> We present herein the data concerning the clinico-pathological and immuno-histochemical features, the method of treatment and the follow-up of our patients.

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## Materials and methods

### Patients

Thirteen cases of follicular centre-cell lymphoma primarily presenting in the skin were analysed. The data were obtained from the records of the Departments of Dermatology and Haematology, University of Florence. Two cases were excluded due to inadequate follow-up information. The patients in this study were seen between 1980 and 1986. In all patients extensive staging procedures were performed, including careful physical examination, biopsies of clinically enlarged lymph nodes and any other extracutaneous lesions, complete blood-cell counts, serum chemistry, chest X-rays, bone marrow biopsies, computerized abdominal tomography and/or abdominal ultrasound and liver spleen scintigraphy. In all patients staging procedures failed to show extracutaneous disease. Adequate follow-up data were available for all these patients.

### Histopathology and immunohistochemistry

Skin biopsies from all patients were in part formalin-fixed, routinely processed and paraffin and plastic embedded. The remainder of the specimen was quickly frozen and stored at  $-70^{\circ}\text{C}$ . Sections from embedded material were routinely stained with H&E, PAS, Giemsa and

reticulin stains. Immuno-histological studies on cryostat sections were performed as described previously.<sup>15</sup> The monoclonal antibodies used in this study and their respective specificities<sup>16,17</sup> are listed in Table 1.

### Therapeutic methods

In nine of 11 patients initial treatment consisted of local orthovolt irradiation (6–8 Gy a week in two fractions, up to 40 Gy;  $20 \times 20$  cm fields; recommended margin for thick tumours 3 cm); in the other two patients radiotherapy was preceded by surgical excision. After relapse, short chemotherapy courses such as CVP (vincristine  $1.4 \text{ mg/m}^2$  i.v. Day 1; cyclophosphamide  $400 \text{ mg/m}^2$  i.v. Days 1–5; prednisone 100 mg p.o. Days 1–5) or a CVP-like regimen plus bleomycin (vincristine  $1.4 \text{ mg/m}^2$  i.v. Days 1 & 8; cyclophosphamide  $300 \text{ mg/m}^2$  i.v. Days 2, 3, 9 & 10; prednisone  $40 \text{ mg/m}^2$  p.o. Days 3–12; bleomycin  $10 \text{ mg/m}^2$  Days 1, 2, 8 and 9),<sup>18,19</sup> were performed in three cases and radiotherapy in the others.

### Statistical methods

Actuarial curves of probability of survival, relapse and extracutaneous spread were calculated using the method of Peto and colleagues.<sup>20</sup> Most were calculated from the time of diagnosis and the actuarial curve of relapse

Table 1. Monoclonal antibodies used

Monoclonal antibody	Cluster of differentiation (CD)	Commercial source	Specificity
OKT3	CD3	ODS, USA	(16)
OKT11	CD2		(16)
OKT4	CD4		(16)
OKT8	CD8		(16)
OKT6	CD1a		(16)
OKT9			(16)
OKM1	CD11b	CC, UK	(16)
B1	CD20		(16)
B2	CD21		(16)
Leu 14	CD22	BD, USA	(16)
Leu M5	CD11c		(16)
HLA-Dr		DP, Denmark	(17)
anti-IgG			(16)
anti-kappa			(16)
anti-lambda			(16)
anti-IgM			(16)
anti-DRC 1			(16)
anti-CD3b receptor			(16)
anti-IgD			(16)

ODS=Ortho Diagnostic Systems;

CC=Coulter Clone;

BD=Becton & Dickinson;

DP=Dakopatts.

probability was calculated from the time of complete remission.

## Results

### *Clinical features*

Clinical data are summarized in Table 2. Eight of 11 patients presented with red to violaceous nodules or tumours, ranging in diameter from 2.5 to 15 cm approximately. They usually had a smooth, shiny surface with little scaling and ulceration (except Case 4). They were surrounded by smaller papular lesions, slightly infiltrated plaques (Fig. 1) and/or gyrate, erythematous lesions. These lesions had been present for periods ranging from 1 to 10 years before the development of rapidly growing skin tumours. Cases 2 and 4 presented isolated lesions

(nodular in Case 2 and tumorous in Case 4), progressing slowly for several months. Cases 6, 7 and 8 presented with small plaques or nodules (less than 1 cm in diameter) (Fig. 2). Small papulonodular lesions, observed either on first examination or at relapse after initial therapy, were biopsied in six patients (Cases 1, 3, 5, 6, 7 and 8). Skin lesions were located on the trunk in all patients; in nine patients they were confined to a circumscribed area on the back.

### *Histopathological findings*

No clear correlation was found between age, clinical morphology of the lesions and the histological growth pattern of the infiltrate. Specimens taken from small, early, plaque-like or papulonodular lesions showed a patchy perivascular and periadnexal or diffuse, band-like

Table 2. Clinical and follow-up data

Patient	Age/sex	Clinical features at presentation	Past history	Initial therapy	Site of relapse	Therapy	Current status	Survival (months)
1	49/F	Large nodule surrounded by papules on the back	Papulonodular lesions for 17 months	RT	Skin after 6 months	RT + COP (– Bleo)	CR	57
2	42/M	Large nodule on the left shoulder	Slowly progressing nodule for 11 months	Excision + RT	—	—	CR	55
3	58/M	Solitary tumour surrounded by slightly infiltrated plaques on the back	Slowly progressing plaque-like lesions for more than 14 years	RT	Skin and axillary lymph node after 9 months	RT + COP	CR	52
4	51/M	Solitary ulcerated tumour on the left flank	Peripherally extending plaques for 7 months	RT	Skin after 23 months	RT	CR	45
5	69/M	Large tumour surrounded by many papules on the back	Slowly progressing papulonodular lesions for 10 years	RT	Skin after 10 months	RT + COP (– Bleo)	CR	39
6	57/M	Multiple small papulonodular lesions on the back	Lesions present for more than 12 years	RT	Skin after 17 months	RT	CR	37
7	39/M	Multiple papulonodular and plaque-like lesions on the back	Lesions present for 5 months	RT	Skin after 9 months	RT	CR	35
8	34/M	Multiple small papulonodular lesions on the back	Lesions present for more than 3 years	RT	Skin after 11 months	RT	CR	19
9	66/M	Large nodule surrounded by annular erythema and plaques on the back	Small papular lesions for more than 2 years	Excision + RT	—	—	CR	16
10	69/F	Large plaque surrounded by papular lesions on the back	Small papular lesions for 8 years	RT	—	—	CR	14
11	61/M	Large tumour surrounded by annular erythema on the back	Small plaques for more than 6 years	RT	—	—	CR	13

COP(–Bleo): Cyclophosphamide, Oncovin, Prednisone (–Bleomycin);

CR: complete remission;

RT: radiotherapy.



Figure 1. Large tumour on the back (Case 5)—the lesion is surrounded by slightly infiltrated plaques.

arrangement of the infiltrate in the upper dermis, sometimes without deep involvement. Specimens obtained from large, late, nodular or tumorous lesions sometimes showed a diffuse cellular infiltrate, extending from the upper dermis into the subcutaneous fat (Fig. 3). In other cases grossly nodular or nodular and diffuse infiltrates were observed. Except Case 4, which showed ulceration, infiltration of tumour cells into the epidermis was never observed and a distinct Grenz zone was always present.

In all lesions the neoplastic infiltrate was composed of

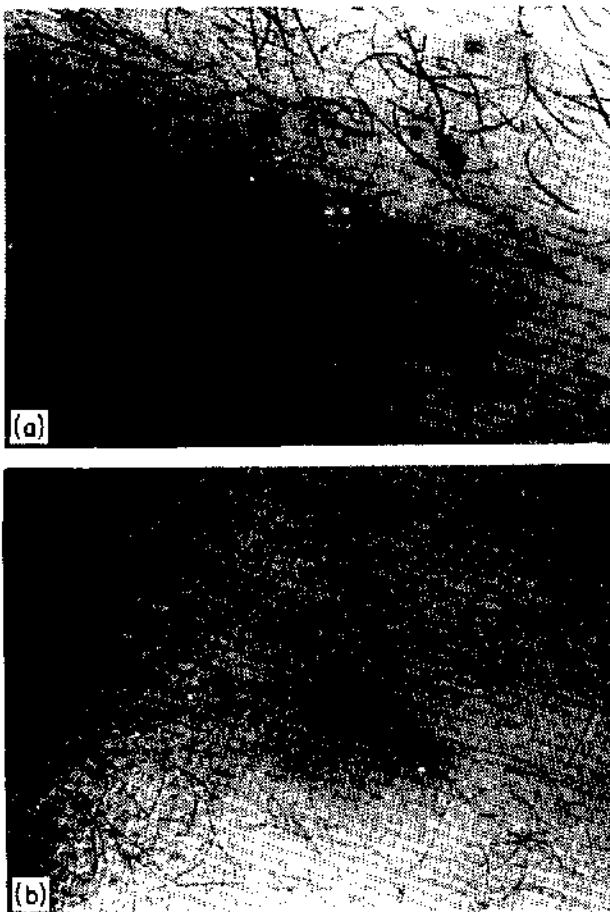


Figure 2. (a) Small nodular lesion (Case 8). (b) small, early plaque-like lesion (Case 6).



Figure 3. View showing a dense cellular infiltrate throughout the dermis. The epidermis is spared (H & E  $\times 36$ ).

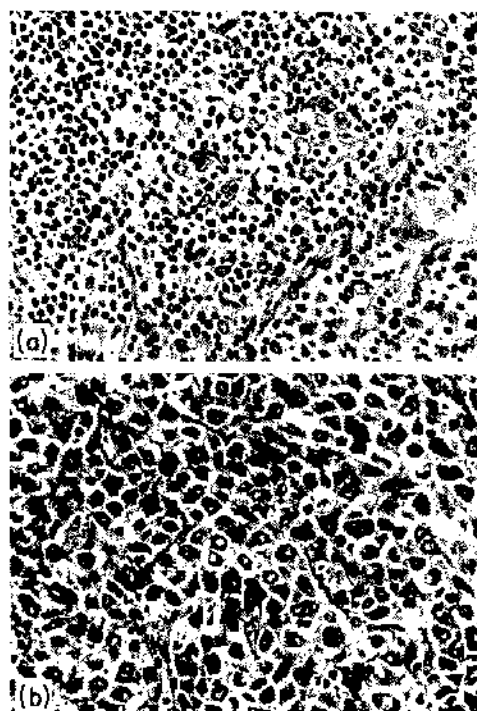


Figure 4. Centroblastic/centrocytic lymphoma; depending on the size of the centrocytes this lymphoma can be classified, according to the working formulation for clinical usage, as either small and large cell (a) or large cell lymphoma (b) (H & E,  $\times 228$ ).

follicular centre-cells (small and/or large cleaved and/or large non-cleaved) (Fig. 4). The relative quantity of each cell type was variable in the different patients, even if the large majority of the neoplastic cells were centrocytic in type (small and/or large anaplastic). The cases were classified according to the diagnosis made at the first biopsy. Referring to the working formulation for clinical usage<sup>21</sup> five patients (Cases 1, 2, 4, 5 and 7) were classified as having large cleaved follicular centre-cell (FCC) lymphomas (centrocytic anaplastic according to the Kiel classification),<sup>22</sup> three patients (Cases 3, 9 and 11) had large cleaved and non-cleaved FCC lymphomas and three (Cases 6, 8 and 10) had mixed small and large FCC lymphomas. These last six cases were classified as centroblastic/centrocytic according to the Kiel classification. In six patients (Cases 1, 3, 4, 5, 7 and 9), a variable proportion of the large anaplastic centrocytes showed multilobed nuclei. The number of admixed large non-cleaved cells, immunoblasts and small lymphocytes was variable. Only in case 11 did centroblasts represent more than 25% of the infiltrating cells. Reactive small lymphocytes were more numerous in small recent lesions than in large, late lesions. Macrophages were often numerous. Eosinophils, neutrophils and plasma cells were few or absent.

Histological examination of enlarged lymph nodes in Cases 5 and 7 showed only signs of hyperplastic lymphadenitis.

Histological examination of an enlarged lymph node showed a diffuse proliferation of large, predominantly cleaved cells, similar to those observed in the skin lesions.

#### *Immunohistochemical findings*

The majority of the infiltrating cells were reactive with B-cell associated monoclonal antibodies B1 and Leu-14 (Fig. 5) and expressed the transferrin receptor



Figure 5. Diffuse positive staining for B1 monoclonal antibody (immuno-peroxidase,  $\times 71$ ).

(OKT9+). Case 9 expressed light chains (lambda). In the other cases the dermal infiltrate did not react with anti-heavy or anti-light chain monoclonal antibodies. Reactive T-cells (CD2+, CD3+) were few and sparse (Fig. 6). Considerable numbers of macrophages (CD11b+, CD11c+) were found scattered among the neoplastic cells. In small, early lesions, neoplastic B-cells were mainly arranged in follicular structures along with DRC-1+ dendritic cells in the upper and mid dermis (Fig. 7). Reactive T-cells, mainly CD8+, and CD1a+ dendritic cells were always numerous in the interfollicular areas, while CD11b+ macrophages were few and dispersed.

#### *Therapy and follow-up data*

The relevant clinical findings, methods of treatment and



Figure 6. Scattered non-neoplastic cells positive for OKT11 monoclonal antibody (immuno-peroxidase,  $\times 71$ ).

follow-up data from the 11 patients are summarized in Table 2. All the patients went into complete remission after initial therapy. Only one patient (Case 3) developed lymph node involvement (simultaneous with a cutaneous relapse) 9 months after complete remission, 11 after the initial diagnosis. Six of 11 patients (54.5%) had a relapse, with a median disease-free period of 15.5 months (Fig. 8). All the patients but one (Case 3) had recurrent disease confined to areas of the trunk close to the site of onset, usually outside the radiotherapy field. In all patients radiotherapy alone (Cases 4, 6, 7 and 8) or associated with short courses of chemotherapy (Cases 1, 3 and 5) led to prompt disappearance of the skin lesions. At the present time, all patients are alive and in generally good health.

### Discussion

We studied 11 patients with follicular centre-cell lymphoma primarily presenting in the skin. They had the clinical and pathological features of Crosti's reticulohistiocytoma,<sup>14</sup> a cutaneous disorder well described in the European dermatological literature<sup>23-25</sup> but hardly seen elsewhere. The nature of the neoplastic cells in this condition has been hotly debated. Both histiocytic<sup>23-25</sup> and T-cell<sup>26</sup> origins have been suggested, but there is now increasing evidence of a B-cell origin.<sup>27-29</sup> Furthermore, the monoclonal nature of neoplastic B-cells has been recently confirmed by molecular gene rearrangement studies.<sup>30</sup>

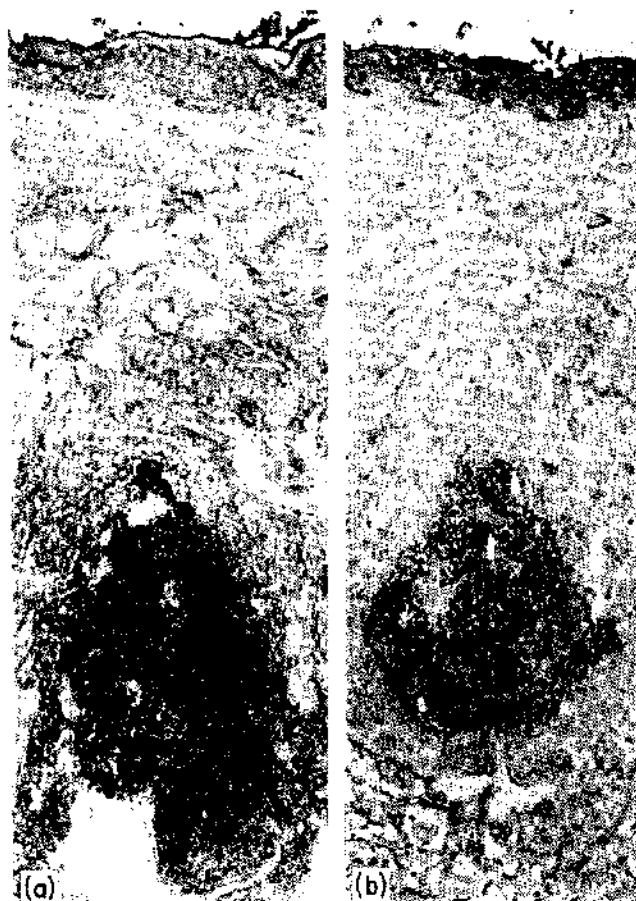


Figure 7. Follicular positive staining for Leu 14 (a) and DRC-1 (b) monoclonal antibodies (immuno-peroxidase,  $\times 92$ ).

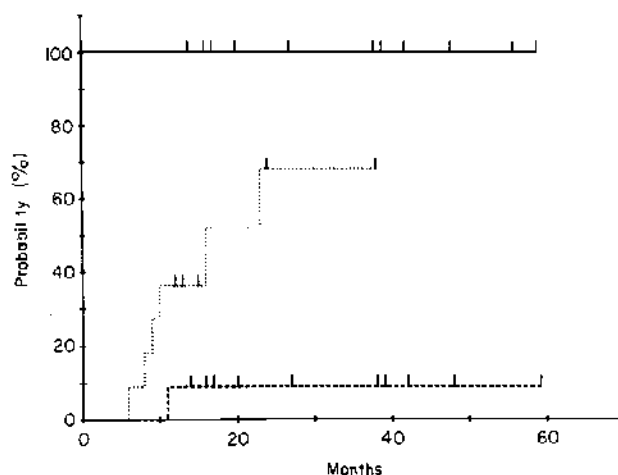


Figure 8. Actuarial survival probability (—), probability of extracutaneous spread of disease (---), and probability of relapse (·····) after complete remission. The small vertical marks represent individual patient's survival or freedom from either relapse or extracutaneous spread for the indicated period.

Our immuno-histochemical data confirm the B-cell nature of this typical cutaneous lymphoproliferative disorder. In fact, the neoplastic cells always showed a CD20+, CD22+ immuno-phenotype. The lack of staining for surface immunoglobulins (sIg) in all patients but one (Case 9) is not surprising and has been reported recently both in lymph nodal<sup>31</sup> and cutaneous FCC lymphomas.<sup>29,32</sup> The absence of an Ig+ staining is presumably due to weak expression of sIg; in fact, more sensitive assays demonstrated an immunoglobulin monoclonal restriction.<sup>30</sup> Histologically, these lymphomas were characterized by a nodular, diffuse or nodular and diffuse dermal infiltrate, with a variable proportion of small and/or large cleaved and/or large non-cleaved cells. According to the working formulation for clinical usage of non-Hodgkin lymphomas<sup>21</sup> five cases were classified as large cleaved FCC lymphomas, three cases as large cleaved and non-cleaved FCC lymphomas and three cases as mixed, small and large FCC lymphomas. In agreement with Willemze and colleagues,<sup>28,29</sup> no substantial clinical, immunological or prognostic differences between these subgroups were observed. This classification has, therefore, limited clinical application at the moment. The reported cases were characterized by a homogeneous clinical morphology, with nodular and tumorous skin lesions and smaller plaque-like or papulonodular lesions confined to a circumscribed area of the trunk. All patients showed a strikingly good and prompt response to treatment, independent of the size of skin lesions, with a low tendency for extracutaneous spread (observed only in Case 3). They are all currently alive and in generally good health. The median disease-free period was 15.5 months, which is shorter than that recently reported by others.<sup>28</sup> This difference might be due to the non-aggressive initial treatment without chemotherapy used in our patients. The lack of extracutaneous spread of the disease in all but one patient, in this instance limited to a single drainage lymph node, strongly supports suggestions of the cutaneous origin of this lymphoma<sup>27-29</sup> and justifies our choice of non-aggressive therapy.

### Acknowledgments

The Authors thank Mr D. Danielli (Istituto di Anatomia e Istologia Patologica, Università di Firenze, Italy) for his skilful technical assistance.

This work was supported by Ita Rian Ministry of Education (University funds, 60%).

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